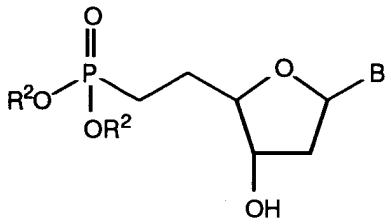
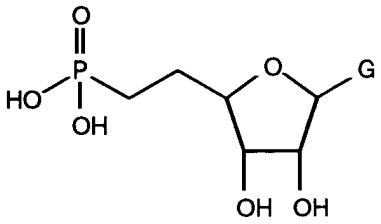
Rejection under 35 U.S.C. § 102(b)

The Office rejected claims 53 and 54 as allegedly anticipated by Martin et al. (*Chem. Abstracts*, (1988) 109:231447m, of record). The Office asserted that the claims recite guanosine 5'-methylenephosphonate. Martin et al. disclose nucleotide analogs having a hydroxyl group at the 2' position. Claims 53-54 recite nucleotide analogs having hydrogen atoms at the 2' position. Martin et al. do not anticipate the claims.



claim 53



Martin et al.

Applicants respectfully request the Office to reconsider and withdraw the rejection.

Rejection under 35 U.S.C. §103

The Office rejected claims 51 and 52 as allegedly prima facie obvious over Chu et al (*Chem. Pharm. Bull.* 37:336-339, 1989, of record, hereafter "Chu") in view of Reist et al (WO84/04748, of record, hereafter "Reist").

Establishing a *prima facie* case requires that the Office provide motivation for one skilled in the art at the time to combine Chu et al. with Reist, and that the results obtained would have been reasonably predictable. The Office's theory is as follows: (a) Chu et al. disclose a problem ("cellular resistance" to therapeutic effect due to the inability of the cells or virus to accomplish the first phosphorylation step) and (b) Reist discloses the answer to the problem (phosphonates bypass this first phosphorylation step).

The Office's statement of the Chu et al. problem is a hindsight concoction. Chu et al. are entirely devoid of any teaching or suggestion that failure of initial phosphorylation of their 2'-F-ara-purines is an obstacle to antiviral utility. On the contrary, the Office's arguments are entirely inconsistent with the Chu et al. results. Chu et al. find that the 2'-F-ara-purines are active against leukemic cells. If initial phosphorylation is a problem "regardless whether the compound is an antiviral or anticancer agent" as the Office states, then why do the Chu et al. compounds work for anticancer purposes? For the Chu et al. compounds to work one would have

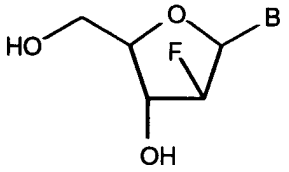
expected the host cells to supply the first phosphorylation - otherwise the compounds could not have possessed the reported anticancer activity. Of course, the Office could postulate that the anticancer utility, unlike the antiviral utility, does not require initial phosphorylation, but this would fly in the face of the Office's conclusion that phosphorylation is required "regardless whether the compound is an antiviral or anticancer agent."

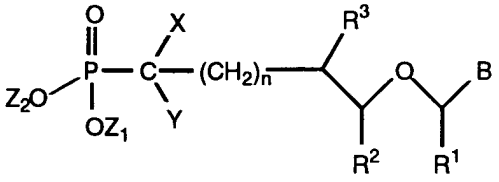
The fact of the matter is that the Chu et al. antiviral failure could have been attributed to a number of causes, e.g., inability of the HSV-1 polymerase to recognize the 2'-arafluoropurine triphosphate as a substrate or failure of cellular uptake, none of which would be solved by resort to a phosphonate analog. The key defect in the *prima facie* case is that there is no way of elucidating from Chu et al. why the viral utility failed and the cancer utility succeeded. Thus, there would have been no reason to have looked to Reist for an answer. This combination of references is a hindsight fabrication.

Published results further show there is no basis to predict antiviral activity of some of the claimed derivatives from the corresponding 2'-arafluoro nucleosides. Borthwick et al. (*J. Med. Chem.*, 34:907-914, 1991, of record) showed that the 2'-arafluoroguanosine nucleoside is active against HSV-1 and HSV-2 (Table II, page 910) while 5'-methylene phosphonate derivative of this nucleoside is inactive against the same viruses, but is active against HCMV and VZV instead (Buhr et al. (*Collect. Czech. Chem. Commun.* 58:102-104 1993, of record, hereafter "Buhr"). Similarly, Reist showed that Vidarabine, i.e., 2'-arafluoroadenosine nucleoside, is active against HSV-1 (Table A, page 35) while 5'-methylene phosphonate derivative of this nucleoside is inactive against HSV-1 (Buhr). Watanabe et al. (*J. Med. Chem.*, 22:21-24, 1979, of record, hereafter "Watanabe") showed that the 2'-arafluorocytidine nucleoside is active against HSV-1 (Table I, page 22) while the 5'-methylene phosphonate derivative of this nucleoside is inactive against tested herpesviruses (Buhr). Watanabe showed that the 2'-arafluorothymidine nucleoside is active against HSV-1 (Table II, page 23) while the 5'-methylene phosphonate derivative of this nucleoside is inactive against HSV-1, but active against EBV (attached Declaration).

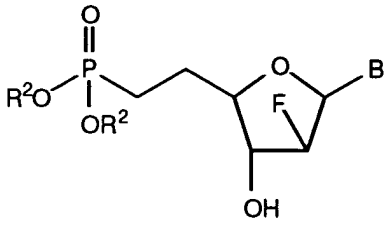
Even if the Chu et al. HSV-1 failure could have been attributed to an absence of initial phosphorylation, *and* the results could have been reasonably predictable,

the combination of references still fails to meet the claims. To arrive at Applicant's claimed compounds, one must select n = 0, X and Y = H from the Reist structure and then superimpose this on the Chu structure.





Chu et al. Reist



claim 51

Reist provides no basis to do this because he expresses no preference for any value of n. One needs to use Applicant's specification to arrive at n = 0. Reist also indicates no preference for X or Y: They may both be H, H and OH or, together, =O. Again, one must use Applicant's specification to pick the structure where X and Y are both H.

The Office asserted in the final action that Reist teaches that the use of the 5'-methylenephosphonate derivatives can aid the agent in crossing the cell membrane. Regarding cellular uptake, and contrary to the Office's assertion, Reist doesn't say anything about phosphonates offering any advantage for cell permeation. The artisan would have expected charged nucleotide analogs to have a *reduced* cell permeation due to the charges on the molecule.

The Office maintained the rejection for reasons given at pages 2-3 of the Office action mailed on February 8, 1995. In that action, the Office asserted that the Reist compounds have the advantage of reduced toxicity. Applicants fail to understand this argument because Reist is silent on the toxicity of his compounds. Reist merely compares the biological properties of two compounds having guanine linked to an open chain phosphonate against the activity of Vidarabine, a nucleoside containing adenine linked to a closed chain sugar with no phosphonate group.

The Office action asserted that Reist teaches the 5'-phosphonate derivatives of the claimed compounds. However, Reist disclosed thousands of compounds and one can only arrive at Applicant's compounds using Applicant's specification as a guide to pick the relevant structures as stated above.

At page 5 of the final action, the Office alleged that Chu taught that 2'-fluoro-araG possesses anticancer activity as stated at page 337, column 2, lines 2-5. Chu states at page 337, column 2, lines 5-7 that the guanine-containing compound is toxic *in vivo*. Taken as a whole, lines 2-7 at the second column of page 337 suggest that one would have expected the claimed guanine-containing compounds to be toxic, not antivirally active, even if one could have found a reasonable basis for combining Chu and Reist. The Office must consider this in evaluating Chu because references must be considered in their entirety and as a whole. *In re Panduit* 1 U.S.P.Q. 2d 1593 (Fed. Cir. 1987).

The Office asserted at page 6 that the Office is focusing on structural changes at the 5' position and their effect on biological activity. Near the bottom of page 6, the Office stated "the exogenous addition of a stable phosphorus group, i.e. the 5'-methylenephosphonate, should also yield a biologically active agent." Applicants pointed out above, Chu showed that the result was unpredictable biological activity because Chu's compounds were biologically inactive as antivirals while having antitumor activity. There was no reason to know why Chu's compounds were inactive as antiviral agents and thus there is no rational basis for predicting biological activity of the resulting molecule. Only Applicant's antiviral data provides the source of a reasonable basis for expecting success.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

The Office rejected claims 51-54 as indefinite because the claims defined the variable R^1, but no R^1 appeared in the chemical structure of claims 51 and 53. Applicants have amended the claims to remove the definition of R^1. The rejection should now be moot.

The Office rejected claims 51 and 53 as indefinite because the claims did not define the abbreviation "$HTEA^+$." Applicants have amended the claims to recite hydrogentriethylammonium ion, which is the definition for $HTEA^+$ at page 8, line 24. The rejection should now be moot.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph

The Office objected to the specification and rejected claims 51-54 as allegedly not supported by an enabling disclosure. The Office asserted at pages 7-8 of the Office action that the specification provided insufficient guidance about which viruses the claimed compounds might have activity against. At page 8, the Office stated "a general statement that the claimed compounds are effective against herpes viruses without any antiviral data showing efficacy against a specific type of herpes virus is deemed inadequate to satisfy the first paragraph of USC 112." Applicants respectfully traverse the rejection because:

1 One of ordinary skill in the art could have identified a herpesvirus without undue experimentation because scientists knew of only a limited number of human herpesviruses;

2 Applicants have provided data showing efficacy against a specific type of herpes virus, i.e., Buhr showed antiviral activity against HCMV for the 2'-deoxyguanosine compound and against HCMV and VZV for the 2'-deoxy-2'-arafluoroguanosine compound; and

3 The claims recite only the active compounds or intermediates in their synthesis.

When Applicants filed the application, scientists knew of six groups of human herpesviruses, see, e.g., *Virology*, vol. 2, 2nd Edition, B. N. Fields et al. editors, Raven Press, New York, 1990, p. 1787-1793, see especially p. 1787, newly cited. The known viruses were HSV-1, HSV-2, VZV, HCMV, Epstein-Barr virus and human herpesvirus 6. Reist, at page 23, lines 21-24 lists HSV-1, HSV-2, EBV, VZV and CMV as herpesviruses. The artisan knew how to propagate and use human herpesviruses for antiviral testing purposes, see e.g., Akesson-Johansson et al.,

Antimicrob. Agents Chemother., 34:2417-2419, 1990, newly cited; Sidwell et al., *Nucleosides Nucleotides*, 8:833-836, 1989, of record. The artisan would look to the activity of a claimed compound against one or more of these viruses as an indicator that the compound could have activity against other herpesviruses. The specification's teaching at page 6, lines 16-29 directs the artisan to herpesviruses and describes an assay for activity against a herpesvirus. At page 33, line 1 through page 34, line 16, Reist described an assay for measuring the antiviral activity of test compounds against HSV-1. Applicant's teaching and antiviral data, coupled with the knowledge of the Artisan satisfied the enablement requirement for how-to-use under Section 112.

Claim 51 recites the 5'-methylenephosphonate derivatives of 2'-deoxy-2'-arafluoroguanosine and the related N^2-isobutyrylguanine and 2,6-diaminopurine compounds. Claim 52 recites only the biologically active guanine base compound. The N^2-isobutyrylguanine is a base-protected intermediate used to make the unprotected biologically active guanine compound, see specification page 28, line 36 through page 29, line 2. The 2,6-diaminopurine compound is also an intermediate for the guanine analog. Studies that workers published before Applicant's filing date showed that enzymes converted 2,6-diaminopurine to guanine (Spector et al., *Biochem. Pharmacol.*, 32:2505-2509, 1983, newly cited), so it would have been apparent to the artisan that the 2,6-diaminopurine compound is at least useful as an intermediate for *in vitro* conversion to the guanine analog.

Claim 53 recites only the 5'-methylenephosphonate derivatives of 2'-deoxyguanosine and the related N^2-isobutyrylguanine and 2,6-diaminopurine compounds. Claim 54 recites only the biologically active guanine base compound and intermediates in its synthesis. Buhr showed that the 2'-deoxyguanosine compound, designated compound **5** in Buhr, had activity against HCMV. The Office implicitly asserted that this compound possessed no anti-herpesvirus activity at all. The EC_{50} data, i.e., the concentration that reduced cytopathic effects by 50%, in Buhr showed that compound **5** had a value of 28.3 μg/mL. The toxicity of **5**, i.e., the IC_{50} value, was greater than 100 μg/mL. Thus, the data showed that **5** had antiviral activity against HCMV and a selectivity index of 3.5. Applicants respectfully request the Office to reconsider its assertion with respect to the 2'-deoxyguanosine compound.

The Office alleged at page 9 of the final action that Applicants did not provide data showing the range of moieties at R^2 that had biological activity when R^2 consisted of a C_{1-12} moiety. Applicants included these R^2 substituents as synthetic intermediates in the synthesis of the fully deprotected nucleotide analogs. For these compounds, R^2 would be hydrogen. The specification described means to synthesize the unprotected compounds, e.g., compound 76 at page 28, lines 12-16 to obtain the deprotected phosphonate moiety and compound 80 at page 28, line 36 through page 29, line 2 to obtain the deprotected guanine base to obtain the fully-deprotected 2'-deoxy-2'-arafluoroguanosine compound. Whatever their inherent activity against viruses, these compounds are demonstrably enabled for use as intermediates in making active antiviral compounds.

Applicants respectfully request reconsideration and withdrawal of the rejection. Applicants believe the application is in condition for allowance and solicit an early Notice to that effect.

Respectfully submitted,

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